Developmental and Reproductive Toxicity of Methyl Isocyanate: Human Data

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Overview

- Exposure to methyl isocyanate (MIC) in Bhopal
  - Basis of the human studies
- Studies
  - Developmental effects
  - Female reproductive effects
  - Male reproductive effects
- Summary of human and animal findings

Exposure to MIC in Bhopal

- Accident in Bhopal, India on December 2-3, 1984 around midnight
- 30 metric tons of MIC escaped in one hour
- Gas spread like a cloud over a densely populated area, 40 km^2
  - ~100,000 people were severely or moderately exposed
  - ~400,000 people were mildly exposed
  - ~2500 – 5000 people died in the 1st 3 days

Exposure to MIC in Bhopal 2

- Mean MIC concentration in gas cloud estimated as 27 ppm
  - TLV is 0.02 ppm
- Additional contaminants unknown
- Exposed via respiratory tract, skin, ingestion of saliva
- Activity level influenced exposure
  - Running in panic to escape led to higher dose

Developmental Effects in Humans

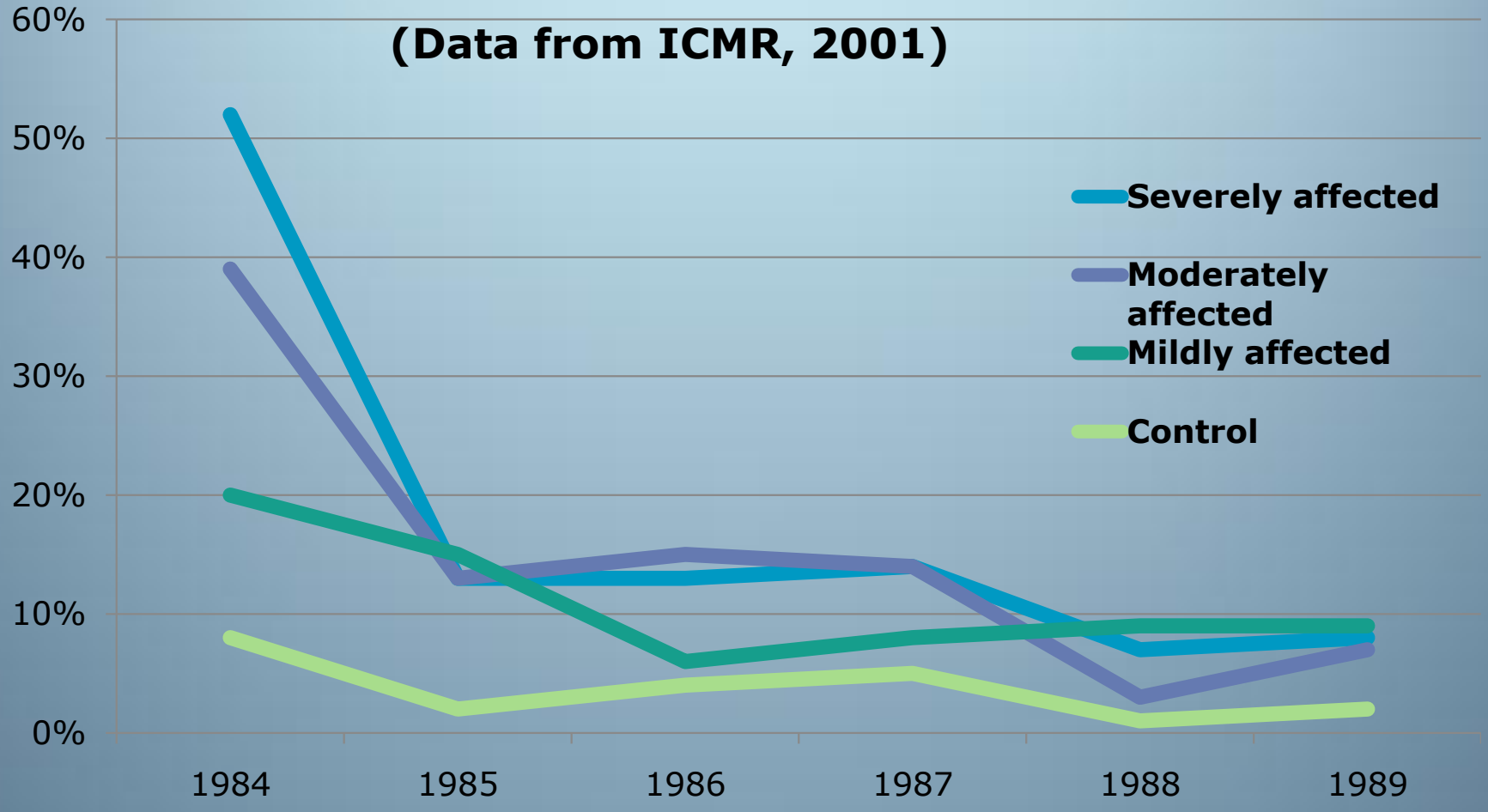
- Eight studies of pregnancy outcome & neonatal mortality
  - Shilotri *et al., 1986*
  - *Varma, 1987*
  - *Kanhere et al., 1987*
  - *Bhandari et al., 1990**
  - *Kapoor, 1991**
  - *Varma, 1991**
  - *ICMR, 2001**
  - *Dhara and Dhara, 2002*
- Two studies of effects after birth in those exposed *in utero*
  - Ranjan *et al., 2003*
  - *Mishra et al., 2009a*

*Presented specific rates for early pregnancy loss

Developmental Effects: Pregnancy Outcome

Study Authors (Year)	Population (# Pregnant Women)	Spontaneous Abortion Rate
Bhandari *et al*. (1990)	Severely affected areas (n=2566) Controls (n=1218)	24% 6%
Kapoor (1991)	Severely affected area (n=75) Controls (n=60)	27% 10%
Varma (1991)	Residence located within 1 km radius of Union Carbide plant (n=638)	59%
Indian Council of Medical Research (ICMR, 2001)	Area of residence: Severely affected (n=195)	52%
	Moderately affected (n=160)	39%
	Mildly affected (n=30)	20%
	Control (n=36)	8%

Pregnancy Outcome – Spontaneous Abortion Rate over Five Years Following Gas Disaster



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Developmental Effects – Neonatal Mortality

- Varma (1987) – Neonatal mortality in those born to exposed mothers was 14.2% compared to up to 3% in the controls
- Bhandari *et al*. (1990) – Perinatal and neonatal mortality significantly elevated ($p<0.001$) in those exposed

Developmental Effects – Postnatal Manifestation

Ranjan et al. (2003) – Physical Growth

- Exposed *in utero*, measured during adolescence
- Covariance model: age, mother's height and weight, father's height and weight, and socioeconomic status
- Found significantly decreased size of males:
  - Weight*
  - Height*
  - Mid-arm circumference*
  - Head circumference*
- Study limited by small number of those exposed *in utero*

* $p<0.005$

Developmental Effects – Postnatal Manifestation

Mishra et al. (2009a) – Immune system

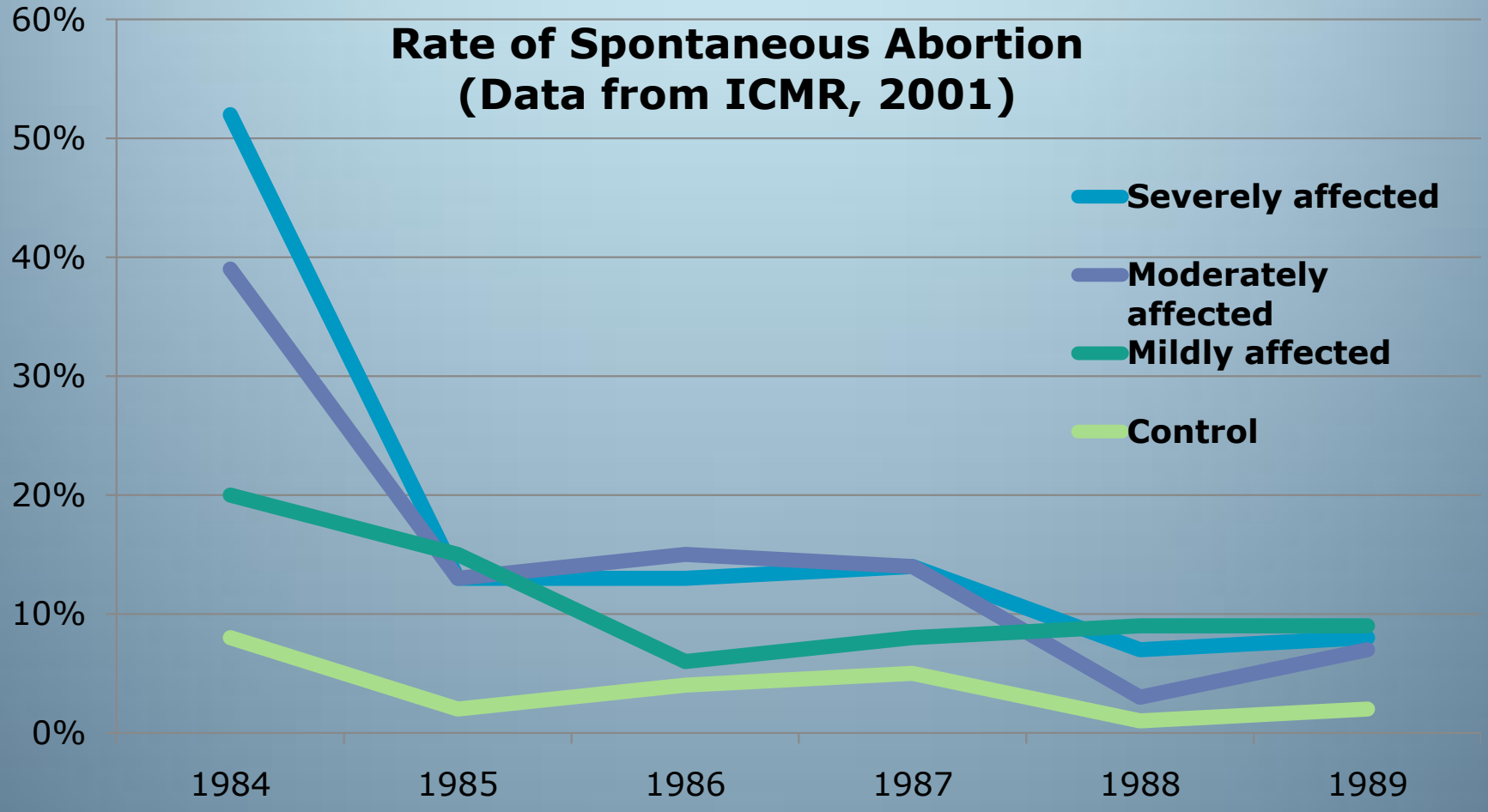
- Exposed *in utero* during the first trimester of pregnancy, immune system function examined 24 years later
- Blood parameters increased in those exposed:
  - B lymphocytes*
  - interleukin (IL) 2 *
  - interferon gamma (IFN- γ) *
  - IL-4 *
  - IL-10 *
  - Immunoglobulin (Ig) A *
  - IgG *
  - IgM *
  - IgE *

* $p<0.001$

Female Reproductive Effects

- Two studies: Menstrual dysfunction, gynecological complaints not related to pregnancy outcome
  - Shilotri *et al*., 1986
  - Dhara and Dhara, 2002 (Medico Friend Circle Study)
- Three review articles: Reproductive health problems in exposed women continue
  - Varma and Varma, 2005
  - Sharma, 2005
  - Mishra *et al*., 2009b
- Eight studies: Pregnancy outcome (described above)

Pregnancy Outcome – Five Years Following Gas Disaster



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Male Reproductive Effects

- Two studies evaluated possible toxic effects on male reproduction: Semen analysis
  - Daniel *et al*., 1987: 18 exposed & 10 control men
  - Deo *et al*., 1987: 19 exposed men (no controls)
- Neither study found significant differences in sperm counts or other parameters measured
- Study limitations:
  - Samples collected 3-6 months after exposure.
  - No definite period of abstinence prior to semen collection
  - Lack of adequate (Daniel et al.) or any (Deo et al.) control for potential confounders (e.g., smoking, alcohol consumption)
  - Small sample numbers for parameters with large variations

Summary of Human Data

- Human data come from the gas disaster in Bhopal
- Multiple studies show adverse impacts on pregnancy outcome
  - These effects persisted over years following the accident
- Postnatal developmental effects seen in those exposed *in utero*
  - Effects on growth, immune function
- Clinicians in field report gynecological problems continue
- No adequate study of male reproductive effects

Integrative Evaluation - Developmental Effects

- Both animal and human studies demonstrate an effect on survival of the exposed conceptus
  - Fetal loss / Spontaneous abortion
  - Neonatal mortality
- Postnatal growth effects
  - Animals – Bone shortening
  - Humans – Shorter stature

Integrative Evaluation - Female Reproductive Effects

- Fetal loss and neonatal mortality in animal and human studies
  - May indicate an effect on female reproduction
  - Continued elevated rates years after exposure in human studies may indicate an effect mediated by female reproductive toxicity
- Both animal and human studies found decreases in placental weight

Integrative Evaluation - Male Reproductive Effects

- Animal data show reversible reduction in mating performance and loss of spermatozoa
  - With no dominant lethal effects
- Human studies were conducted too late to detect a transient effect on spermatogenesis

ANY QUESTIONS?